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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,743	07/21/2003	David T. Hung	12.026011-DIV	4720
38732	7590	11/07/2006	EXAMINER	
CYTYC CORPORATION 250 CAMPUS DRIVE MARLBOROUGH, MA 01752			SANG, HONG	
			ART UNIT	PAPER NUMBER

1643

DATE MAILED: 11/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/622,743	Applicant(s) HUNG, DAVID T.	
	Examiner Hong Sang	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 September 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 13, 14, 17, 18, 25, 26 and 29 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 13, 14, 17, 18, 25, 26 and 29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

RE: Hung

1. Applicant's response filed on 9/8/2006 is acknowledged. Claims 1-12, 15, 16, 19-20, 21-24, 27-28 and 30-40 are cancelled. Claims 13, 14 and 26 are amended. Claims 13, 14, 17-18, 25-26 and 29 are pending.
2. Claims 13, 14, 17-18, 25-26 and 29 are under examination.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections Withdrawn

4. The objection to the specification because the first line of the specification was not updated to reference the earlier filed applications is withdrawn in view of applicant's amendment to the specification.
5. The objection to the specification because it contains an embedded hyperlink and/or other form of browser-executable code is withdrawn in view of applicant's amendment to the specification.
6. The objection to claim 14 as it contains non-elected inventions is withdrawn in view of applicant's amendment to the claim.
7. The objection to claim 16 as being a duplicate of claim 14 is withdrawn in view of applicant's cancellation of the claim.

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Rejections Withdrawn

8. The rejections of claims 26 and 29 under 35 U.S.C. 112, second paragraph for lack of antecedent basis are withdrawn in view of applicant's amendment to the claims.

9. The rejection of claims 13, 14, 16-18, 25, 26 and 29 under 35 U.S.C. 103(a) as being unpatentable over US Patent No.6,221,622 B1 (data of patent: 4/24/2001, effective filing date at least 4/28/1998, IDS) in view of Love et al. (Lancet 1996, 348: 997-999, IDS) and US Patent No. 6,287,790 B1 (Data of Patent: 9/11/2001, effective filing date 11/30/1998) is withdrawn in view of applicant's amendment to claim 13.

10. The rejection of claims 13, 14, 16-18, 25, 26 and 29 under 35 U.S.C. 103(a) as being unpatentable over US Patent No.6,494,859 (data of patent: 12/17/2002, effective filing date 4/28/1998) in view of Love et al. (Lancet 1996, 348: 997-999, IDS) and US Patent No. 6,287,790 B1 (Data of Patent: 9/11/2001, effective filing date 11/30/1998) is withdrawn in view of applicant's amendment to claim 13.

Response to Arguments

11. The rejection of claims 13, 14, 17-18, 25, 26 and 29 under 35 U.S.C. 103(a) as being unpatentable over JAMA (1973, 224(6): 823-827, IDS) in view of Love et al. (Lancet 1996, 348: 997-999, IDS), Hou et al. (Radiology, 1995, 195 (2): 568-569, IDS) and US Patent No. 6,287,790 B1 (Data of Patent: 9/11/2001, effective filing date 11/30/1998) is maintained.

The response states that JAMA (Sartorius) does not teach or suggest all of the limitations of the present claims including the use of a single lumen catheter as well as determining the presence of a marker in a fluid sample. Love teaches a method of using endoscopy to study stages of cancerous breast disease. Love does not teach or suggest the use of a single lumen catheter to introduce and remove wash fluid from a breast duct. In fact, as pointed out by the Examiner (Office Action page 8), Love teaches away from the use of a catheter to remove ductal washings because as stated in Love et al. "...the duct is so small...that it is difficult to aspirate back through the cannula to obtain material. When washing, we removed the catheter and collect the fluid externally in a capillary tube." (page 998, 2nd paragraph). Thus, Love does not teach or suggest the use of a single lumen catheter to introduce and remove wash fluid from a breast duct, as well as examining the ductal fluid sample to determine the presence of a marker. Hou teaches a method of duct cannulation for galactography before excision of a patient's breast. Hou does not teach or suggest the use of a single lumen catheter to introduce and remove wash fluid from a breast duct for the purpose of analyzing the contents of the wash solution. US Patent No. 6,287,790 issued to Lelievre, et al. teaches the localization of nuclear apparatus proteins (NuMA) to identify tumor cells and different stages in the tumor progression and differentiation processes. Lelievre does not teach or suggest that the presence of NuMA in a ductal fluid sample can be used as a marker for determining a cancerous or precancerous condition in the breast of a patient. Lelievre merely examines the localization of NuMA within cell lines. The Examiner has failed to establish a prima facie case of obviousness, since Sartorius,

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Love, Hou, or Lelievre alone or in combination, fail to teach or suggest the claimed invention and further fail to provide the necessary motivation or expectation of success for the ordinarily skilled artisan to arrive at the claimed invention. The Examiner has failed to meet the burden of providing evidence of a motivating force sufficient to impel a person of ordinary skill in the art to combine the teachings of Sartorius, Love, Hou or Lelievre to arrive at the claimed invention. First, neither Sartorius nor Love teach or suggest a method of introducing and retrieving a sample from a breast duct via a single lumen catheter. In fact, Love specifically teaches that the use of a single lumen catheter does not work when trying to aspirate a sample back through a catheter disposed within a duct of a breast and thus a different methodology had to be used to obtain a sample. Hou et al. does not teach or suggest the introduction and retrieval of a ductal lavage solution from a duct through a catheter. Hou teaches a method for introducing a dye into a breast duct solely for the purpose of galactography. Once the dye has been introduced and the galactography procedure is finished, the dye is removed and discarded. There is nothing in Hou et al. that teaches or suggests that the dye removed from the duct after the procedure is over contains any cellular material or markers that would be useful in detecting cancer or precancer. Love specifically teaches that the use of a single lumen catheter does not work when trying to aspirate a sample back through a catheter disposed within a duct of a breast. Hou teaches the removal of dye from a breast duct during a completely different procedure. Why would one of skill in the art believe that the teaching of Hou, using a completely different and unrelated methodology, would provide a greater expectation of success than the

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teaching of Love which is directly on point and unequivocally states that the aspiration of solution from a duct through a catheter does not work? Neither Sartorius nor Love teach or suggest detecting the presence of a cancer marker in the isolated ductal fluid. Sartorius mentions that the testing for elevated levels of the enzyme reverse transcriptase may be implicated as a possible cancer marker. Thus, the presence of reverse transcriptase in a fluid sample is used in Sartorius to classify women who are at "high risk" of getting breast cancer. As mentioned in Sartorius, women who use oral contraceptives have high titers of reverse transcriptase but they do not necessarily have cancer. Thus, the "marker" used in Sartorius is not used to determine the presence of cancer in a patient. Love uses positive membrane neu immunoreactivity, positive nuclear p53 immunoreactivity or aneuploidy to confirm a previous diagnosis of DCIS. The "markers" as taught in Love et al. were not used for identifying a patient having breast cancer or breast precancer. Lastly, Lelievre does not teach or suggest that NuMA is a breast cancer marker that can be used to identifying a patient having breast cancer or breast precancer. Lelievre teaches the use of NuMA as a marker for examining the different stages in the breast tumor progression. There is simply no teaching or suggestion in Lelievre that NuMA could be used as a diagnostic marker for the presence of cancer. Thus, the Examiner's argument that NuMA is a breast cancer marker that can be used to identify breast tumor cells is not supported by the evidence. Therefore, Sartorius, Love, Hou, and Lelievre, alone or in combination, fail to teach or suggest a method for identifying a patient having breast cancer or breast precancer comprising placing a ductal access tool comprising a single lumen in a breast duct of a

patient; infusing a fluid into the duct through the single lumen; retrieving a ductal fluid sample from the accessed duct through the single lumen; and examining the ductal fluid sample to determine the presence of a marker comprising an expression product of a gene encoding a nuclear matrix protein, as recited in the claims.

Applicant's arguments have been carefully considered but are not persuasive. Both Sartorius (see page 823, left column, 4th paragraph, and page 827, left column, 3rd and 5th paragraphs) and Love (see page 997, right column under methods) teach use of a catheter to introduce a wash fluid to a breast duct, collecting washings from the ducts, analyzing the washings and determining the presence of cancer cells or precancerous cells by detecting markers such as reverse transcriptase, positive membrane neu immunoreactivity, positive nuclear p53 immunoreactivity or aneuploidy. The catheters of Sartorius and Love comprise a single lumen. While neither Sartorius nor Love teach retrieving ductal wash fluid from the accessed duct through lumen of the catheter, these deficiencies are made up for in the teaching of Hou. Hou teaches a method of infusing a small volume of sterile, water soluble contrast material into the breast duct, and aspirating the contrast solution from the duct through the catheter (see page 568, middle column, last paragraph and right column, 1st paragraph). Applicants argue that Love teaches away from use of a single lumen catheter to introduce and remove wash fluid from a breast duct. Contrary to applicant's assertions, Love does not teach away from the instant invention. While Love teaches that it is difficult to aspirate back through the cannula to obtain material, Love also points out that collecting washings externally after removing the catheter is not optimal and other methods such as a double-lumen

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tube is being developed to overcome this difficulty (see page 998, right column, 2nd paragraph). Therefore, the teachings of Love suggest that retrieving the ductal washings through the lumen is a preferred method to collecting the washings externally. However, Love encountered technical difficulties to do so. The teachings of Hou overcome Love's technical difficulties. Therefore, it would have been *prima facie* obvious and one skilled in the art would have been motivated, in view of the teachings of Hou, to modify the method of Love to introduce and retrieve a wash fluid through lumen of a catheter because Love wanted but failed to do so and Hou has overcome Love's technical difficulties. Applicants further argue that the method of Hou is not for the purpose of analyzing the contents of the wash solution. This argument is not persuasive. While the method of Hou is not for the purpose of analyzing the contents of the wash solution, it does provide a solution for Love's problems. A prior art reference is analogous if the reference is in the field of applicant's endeavor or, if not, the reference is reasonably pertinent to the particular problem with which the inventor was concerned. In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Moreover, The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See, e.g., In re Kahn, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). Applicants further argue that Hou does not teach or suggest that their method would be useful in detecting cancer or precancer. This is not found persuasive because one cannot show nonobviousness by attacking

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references individually where the rejections are based on combinations of references. In *re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In *re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Furthermore, in contrary to applicant's assertions that neither Sartorius nor Love teach or suggest detecting the presence of a cancer marker in the isolated ductal fluid, Sartorius teaches detection of reverse transcriptase in the ductal fluid and reverse transcriptase is known as a possible cancer marker (see page 827, left column, 5th paragraph), and Love teaches detection of marker such as neu-immunoreactivity, positive nuclear p53 immunoreactivity or aneuploidy, which have been shown to be able to confirm the presence of DCIS cells. Applicants argue that women who use oral contraceptives have high titers of reverse transcriptase but they do not necessarily have cancer and therefore, the "marker" used in Sartorius is not used to determine the presence of cancer in a patient. This is not found persuasive the fact that the marker of Sartorius cannot be used to diagnose a subpopulation (women who use oral contraceptives) for the presence of breast cancer does not indicate it would not be a diagnosis marker because no diagnosis marker or treatment is perfect and suitable for any and all populations. While Neither Sartorius nor Love teach detection of NuMA in the ductal fluid, in view of the teachings of Lelievre that NuMA can be used to identify tumor cells and different stages in the breast tumor progression and differentiation process (see abstract), and proliferating non-malignant and malignant mammary epithelial cells show significantly different nuclear distribution of NuMA protein, and further in view that cancer epithelial cells are present in the ductal wash fluid, one skilled in the art would have been motivated to modify the method of

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Sartorius or Love to detect NuMA in the ductal fluid for diagnosis of breast cancer.

Applicants argue that markers of Sartorius, Love and Lelievre are not useful for detecting breast cancer or precancer. This is not persuasive because the last active step of the method (see claim 13) is examining a ductal fluid sample to determine the presence of a marker comprising an expression product of a gene encoding a nuclear matrix protein, the combination of the references teach detect cancer markers, including NuMA in a ductal fluid, therefore, the references teach every limitation of the claim.

Finally, one of ordinary skill in the art would have a reasonable expectation of success to detect NuMA in a ductal fluid because Sartorius and Love teach a method of isolating ductal fluid by ductal lavage, Love teaches that the ductal fluid contains cancerous epithelial cells, Hou teaches a method of obtaining ductal fluid from the breast duct by retrieving the fluid through lumen of a catheter, and Lelievre teaches a method of detecting NuMA in breast epithelial cells using a NuMA specific antibody. Because of these reasons, the rejection is deemed proper and therefore maintained.

Conclusion

12. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the

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shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Hong Sang, Ph.D.
Art Unit 1643
Oct. 30, 2006


CHRISTOPHER H. YAEN
PRIMARY EXAMINER